Case Report

The inner and outer of our thorax: silicone breast implants and pulmonary alveolar proteinosis

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Pulmonary alveolar (phospholipo)proteinosis (PAP) is a rare lung disease, predominantly autoimmune in nature. This case report describes a patient with insidious dyspnoea since 5years and a milky appearance of her bronchoalveolar fluid, leading to the diagnosis of PAP. The onset of symptoms coincided with an exchange of her silicone breast implants. Giant cell reaction in axillary adenopathies pointed towards silicone leakage. Adjuvants, such as silicone, might boost pre-existing antigen reactions of the immune system, potentially leading to autoimmune phenomena.

Keywords: Pulmonary alveolar proteinosis, Autoimmunity, Silicone, Autoimmune/inflammatory, Syndrome induced by adjuvants

Introduction

Pulmonary alveolar (phospholipo)proteinosis (PAP) is a rare, diffuse lung disease characterised by the abnormal accumulation of surfactant in the distal air spaces. The disease was first described in 1958 by Rosen *et al.* There are three different forms of PAP recognised: hereditary, secondary and the acquired PAP. To date, the molecular pathogenesis in over 90% of cases is elucidated. Disruption of the GM-CSF (granulocyte macrophage-colony stimulating factor) signalling, caused by a real or functional deficiency of GM-CSF, avoids the terminal differentiation of the alveolar macrophages. As a result, clearance capacity for surfactant is disturbed and surfactant will accumulate in the alveoli. This leads to respiratory insufficiency while the lung architecture remains preserved.

Case Report

A 47-year-old woman was referred to our outpatient clinic with a persistent, non-productive cough since 5 years. Within the last few months, she also developed dyspnoea, with decreased exercise tolerance and fatigue. Now and then, she suffered from arthralgias and morning stiffness for about half an hour. Besides a history of Raynaud's phenomenon, there were no other elements pointing to a connective tissue disease. At the time of presentation, she was still smoking. With the exception of this 15 pack-year smoking history, no other significant exposures were uncovered in her past medical history. She had a bilateral silicon breast implantation 16 years ago, which was revised and exchanged 10 years later for unknown reason.

On physical examination, we noticed normal vital signs and an oxygen saturation 94% while breathing room air. Her lungs had bilateral fine crackles at the bases. At the left anterior axillary fold, she had markable palpable adenopathies.

Complete blood count did not show any irregularities. Inflammatory parameters and lactate dehydrogenase level (LDH) were normal. Screening for autoimmunity was negative and immunoglobulins were normal.

Lung function tests revealed an isolated decreased diffusing capacity (DLCO 40%).

High-resolution computed tomography (HRCT) of the chest showed patchy ground-glass opacification with interlobular septal thickening with a predominantly central somewhat geographical distribution ('Crazy paving pattern') (Figure 1).

A bronchoscopy was macroscopically normal. Bronchoalveolar lavage (BAL), however, showed turbid fluid and analysis revealed a decreased

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Figure 1 Coronal reconstruction of high-resolution computed tomography (HRCT) of the chest: patchy ground-glass opacification with interlobular septal thickening with a predominantly central somewhat geographical distribution ('Crazy paving pattern').

number of macrophages (75%; normal range 90–100%). There was an increase in CD4- and CD8-cell counts, with a CD4/CD8-ratio of 1.3.

PET-CT confirmed the presence of fluorodeoxyglucose-avid adenopathies at the left axilla. Excision biopsy of these adenopathies showed on microscopic evaluation a giant cell reaction of the foreign body type with multiple fatty infiltrates and vacuoles, suggestive of silicone leakage.

Consequently, the breast implants were excised. Histology of the scar tissue also demonstrated the presence of giant cells.

Discussion

The discrepancy between the mild clinical presentation with insidious onset of dyspnoea and the important radiographic findings compatible with crazy paving pattern, in combination with the findings on BAL fluid (the opaque and milky appearance of the bronchoalveolar fluid with low macrophage counts, high CD4- and CD8-counts), led to the diagnosis of PAP.

As mentioned in the Introduction section, there are three different forms of PAP recognised: hereditary, secondary and the acquired PAP.[1] Acquired PAP is also called autoimmune or idiopathic pulmonary alveolar (phospholipo)proteinosis (iPAP) due to the strong association with high levels of neutralising GM-CSF autoantibodies, responsible for the pathogenic cascade of surfactant accumulation. Although not routinely tested for, these antibodies are known as a highly sensitive and specific diagnostic tool for autoimmune PAP.

Idiopathic pulmonary alveolar (phospholipo)proteinosis represents the vast majority of cases (90%), though the prevalence is estimated at only six to seven individuals per million in the general population. Acquired PAP typically presents at the age of 30–50 years, with a male to female ratio of 2 : 1, presumably caused by the association with smoking.

Silicone-based breast implants have been used since the 1960s for both cosmetic augmentations and reconstructive surgery. Since the beginning, their local and systemic adverse effects remain of great concern.

Around the implant, a fibrous capsule, rich in collagen, is usually formed. Silicone leakage in and through the fibrous envelope are well described with progressing implant age (with or without rupture of the implant). Once outside the capsule, the silicone particles may disperse through soft tissue, lymph nodes, or the vasculature to distant sites.[2]

Homolateral axillary localisations of silicone particles are frequently described, with comparable histological findings to our case.[2]

Post-mortem analysis of 15 individuals with breast implants, performed by Barnard *et al.*, showed significantly more silicone particles in the breast tissue, lymph nodes and abdominal fat, in comparison to individuals without breast implants. No significantly different amounts of silicone particles were found in the lungs, spleen and liver. As such, there are no arguments for direct exposure of silicone to the lungs.

The question has been raised whether this patient has two co-incidental diagnoses or whether a correlation between these two entities (iPAP and silicone leakage) can explain the whole clinical picture.

The extensive literature concerning a correlation between autoimmunity and silicone breast implants demonstrates the controversy and the ongoing debate. The inertia of the silicone particles has been challenged.

Antisilicone antibodies

In different studies, higher levels of serum antisilicone antibodies were measured in implanted women compared to almost none in non-implanted women. [3]

Autoantibodies

After leakage of the silicones, contact with native tissue may cause denaturation of tissue macromolecules such as fibrinogen. The denatured molecules may be recognised as foreign and as such triggering the immune system in genetically susceptible persons. The resulting autoantibodies may probably cross-react with other substrates.[2]

Immunopathologic studies contradict each other in light of possible evidence for higher prevalence of

autoantibodies in implanted women than controls. The difference in outcome is probably due to different study designs, technical issues, patient selection criteria or ascertainment bias.[4] Moreover, if the scientific evidence for a higher prevalence of autoantibodies in implanted women would be solid and sound, the clinical importance is not yet clear

Well defined autoimmune disease

Hennekens *et al.* showed in a large cohort study, based on self-reported symptoms of approximately 11 800 implanted women, a relative risk of 1.25 (95% CI: 1.08–1.41) for all defined connective tissue diseases.[4]

In 2000, Janowsky *et al.* concluded in their meta-analysis of 20 cohort, case–control and cross-sectional publications that the risk was only 0.8 (95% CI: 0.62–1.04) for defined connective tissue disease following silicone breast implantation. The study of Hennekens *et al.* was not included because they used self-reporting of diseases.[3,4]

The potential higher risk of developing a well defined connective tissue disease among silicone-exposed individuals remains a point of discussion, mentioning the same methodological pitfalls.

Undefined autoimmune disease

Shoenfeld *et al.* described ASIA, an autoimmune/inflammatory syndrome induced by adjuvants. He stated that adjuvants, such as silicone, boost pre-existing antigen reactions of the immune system. He linked this to aspecific symptoms like arthralgia, fatigue, etc.[4]

Vasey *et al.* and Fryzek *et al.* reported statistically significant increases in less specific symptoms like arthralgia, fatigue and others after silicone-breast implantation.[4]

A smaller, prospective study by Constant *et al.* concluded that 1 year after breast implantation, patients had more undefined complaints indicative of underlying autoimmune disease, which were not present before surgery.[5]

A relationship between silicone-breast implants and yet non-defined autoimmune phenomena seems plausible, although scientific evidence is still lacking.

Conclusion

Our 47-year old patient presented with respiratory and systemic complaints and a history of exchanged silicone-breast implants.

Her clinical presentation, radiographic findings and BAL fluid results matched the diagnosis of autoimmune PAP. Silicone leakage led to a local inflammatory response, which was confirmed by histological findings of foreign body reaction in the axillary PET-avide lymph nodes. Raynaud's phenomenon, arthralgias and fatigue suggested an autoimmune disease. Taken all together, a systemic (auto)immunological response triggered by silicone leakage could explain the whole clinical picture.

Review of the literature pinpointed some potential pathways for generalised autoimmune responses after silicone leakage. A (causal) relationship between silicone implant and autoimmunity is still very doubtful. Some evidence suggests a higher frequency of undefined complaints probably indicative of underlying autoimmune disease in implanted women. We found no literature concerning the direct association between silicone leakage and iPAP. Prospective, well designed trials could at time lead to definitive answers. Regarding the low frequency of the entity iPAP in contrast to more frequent autoimmune diseases, this could be a challenging task.

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Ethics approval

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